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Pulsatile haemodynamic parameters are predictors of survival in paediatric pulmonary arterial hypertension

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ABSTRACT

Background: There is a need for reliable prognostic parameters in pulmonary arterial hypertension (PAH), especially in children. Pulsatile components of the right ventricular afterload, represented by pulmonary arterial compliance (PACi) and pulmonary stroke volume (PSVi), may provide important additional prognostic information to conventional static haemodynamic parameters. The aim of this study was to determine the prognostic value of PACi and PSVi in paediatric PAH.

Methods: Right heart catheterization data of 52 consecutive paediatric idiopathic/hereditary PAH and PAH associated with congenital heart disease patients with full haemodynamic evaluation seen at the Dutch national referral centre for paediatric pulmonary hypertension between 1993 and 2010 were reviewed. A control group was composed of patients with normal pulmonary vascular resistance. PSVi and PACi were calculated and tested for predictive value for transplant-free survival.

Results: PAH patients had significantly lower PSVi and PACi compared to control patients. PSVi and PACi were lower in patients with higher WHO-functional class compared to those with lower functional classes. Higher PSVi, PACi and mSAP and lower mPAP/mSAP and heart rate were associated with improved survival, independent from WHO-functional class and PAH-targeted therapy. In multivariate analyses PSVi, heart rate and mSAP emerged as the strongest haemodynamic predictors of survival. The effect of vasodilator challenge on the haemodynamic variables did not provide additional prognostic information.

Conclusions: The parameters of both the pulsatile and static pulmonary circulations are strong independent predictors for transplant-free survival, and therefore can be of complementary value in assessing disease severity, predicting survival and guiding treatment in paediatric PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a disease characterized by pulmonary vascular remodelling, leading to severe elevation of right ventricular afterload, ultimately resulting in right ventricular (RV) failure and death. Despite emerging treatment options, PAH is a progressive disease and data on its diagnosis, treatment and outcome is limited, especially in children [1]. In PAH, treatment decisions are based on the assessment of disease severity and prognosis by the use of prognostic (surrogate-) parameters [2,3].

There is a strong need for reliable prognostic parameters that can be used as clinical endpoints in order to guide the treatment of PAH. The currently used parameters are far from perfect, especially in young children with PAH. The World Health Organization functional class (WHO-functional class) and 6-minute walk distance (6-MWD) are recognized as valuable prognostic parameters that are recommended to be used in goal-oriented treatment strategies in adult PAH-patients [4–7]. In children, however, both parameters are often less reliable or not feasible because of young age and/or impaired development [8]. Haemodynamic parameters, such as pulmonary vascular resistance (PVR), and mean pulmonary arterial pressure (mPAP), are important objective measurements used to confirm the diagnosis of PAH. Furthermore, they may provide prognostic information. However, while invasive haemodynamic evaluation in children frequently requires general anaesthesia,

Abbreviations: 6-MWD, 6-minute walk distance; CI, cardiac index; HR, hazard ratio; IPAH/HPAH, idiopathic or hereditary pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; NO, nitric oxide; O2, oxygen; PAC(i), pulmonary arterial compliance (index); PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PP, pulse pressure; PSV(i), pulmonary stroke volume (index); PVR(i), pulmonary vascular resistance (index); Qpi, pulmonary flow index; RV, right ventricle; VO_2, oxygen consumption; WHO-class, World Health Organization functional class.

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the correlation of mPAP and PVRi with clinical status and survival is limited [5,9–14].

Elevated RV afterload leading to RV failure is the main determinant of mortality in PAH. RV afterload consists of static components (PVR and mPAP) defining net forward flow, and pulsatile components defining flow and pressure oscillations. Pulsatile components include pulmonary arterial compliance (PAC), the ability of pulmonary arteries to accommodate oscillatory changes in volume, and pulmonary stroke volume (PSV), the amount of blood ejected in the pulmonary artery per cardiac cycle. The latter differs from RV stroke volume in the setting of intracardiac shunt or tricuspid regurgitation. Conventional haemodynamic parameters such as mPAP and PVRi only partially represent RV afterload, since they represent its static components and ignore its pulsatile components [9,15]. In healthy subjects the pulsatile components contribute little to the RV afterload, due to the low resistance and high compliance of the pulmonary circulation. However in PAH their contribution to RV afterload becomes increasingly important due to arterial stiffening and increased reflection waves [16,17]. PAC and PSV, both reflecting pulsatile components of the RV afterload, may therefore provide additional prognostic information in PAH.

Previous findings in adult PAH patients indicated that PAC and PSV may be valuable predictors for prognosis in adult PAH [18–21]. In paediatric PAH, PAC has previously been shown to be associated with pulmonary vascular disease severity, however its prognostic value for mortality is not clear [22–24]. The purpose of this study was to determine the prognostic value of PSV and PAC in children with idiopathic/hereditary PAH (IPAH/HPAH) and PAH associated with congenital heart disease (PAH-CHD).

2. Methods

In the Netherlands, all paediatric PAH patients are referred to the University Medical Centre Groningen, the national referral centre within the Dutch National Network for Paediatric Pulmonary Hypertension. At the referral centre, the diagnosis of PAH is confirmed by heart catheterization, treatment strategies have evolved according to the 'ESC guidelines for the diagnosis and treatment of PAH', and all patients are regularly seen at standardized follow-up visits [2].

We retrospectively reviewed the diagnostic heart catheterization data of all paediatric patients with IPAH/HPAH and PAH-CHD seen at the Dutch national referral centre from 1993 to 2010. PAH was defined as elevated mPAP ≥ 25 mmHg at rest, with a pulmonary capillary wedge pressure (mPCWP) ≤ 15 mmHg and elevated PVRi ≥ 3 Wood units · m^2 measured during heart catheterization. Only patients who had a full baseline haemodynamic assessment by heart catheterization were included in the study. PAH-CHD patients were subdivided into three different groups, based on their circulatory physiology: 1) patients with an unrestricted pre-tricuspid shunt (atrial septal defects); 2) patients with an unrestricted post-tricuspid shunt ([atrio]ventricular septal defects, patent ductus arteriosus, or uncorrected univentricular heart with unobstructed pulmonary blood flow) and 3) patients with surgically corrected post-tricuspid shunt (without residual shunts) in whom PAH developed or persisted after shunt-closure.

A control group, which was age- and shunt-matched in order to rule out both age and circulatory physiology as possible confounding factors, was composed of patients with low pulmonary vascular resistance (PVRi < 2.5 WU.m^2), catheterized at the University Medical Centre Groningen. The control group included control patients with normal pulmonary circulation (patients with aortic stenosis) and shunt control patients with increased pulmonary blood flow index (Qpi/Qsi > 1.2) due to persistent ductus arteriosus, or atrial septal defects, with normal mPAP (< 20 mmHg).

Our institutional human research committee approved the protocol for the Dutch national clinical patient registry and the use of its data for observational studies. Patients or their legal guardians provided informed consent. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.1. Baseline evaluation

Baseline evaluation included WHO-functional class and diagnostic heart catheterization. Baseline haemodynamic measurements included mean right atrial pressure (mRAP), mPAP, pulmonary arterial pulse pressure (PP), mPCWP, PVR indexed for body surface area (PVRi), Qpi, pulmonary stroke volume index (PSVi) and pulmonary arterial compliance index (PACi). Qpi was determined by using Fick's method, based on estimated oxygen consumption (VO_2). VO_2 was estimated by using two methods: (i) for patients <7 years of age $VO_2 = 1.39 \times \text{Height(cm)} + 0.84 \times \text{Weight(kg)} - 35.7$ and (ii) for patients >7 years of age by the tables of Lafarge and Miettinen [25,26]. PVRi was determined by dividing the pulmonary arterial to venous pressure fall by Qpi. The PSVi was determined by dividing Qpi by the heart rate, and finally PACi was calculated by dividing PSVi by PP.

During heart catheterization, acute vasodilator challenge was performed by using inhaled nitric oxide (NO), or NO with 100% O_2. In the case of sequential pulmonary vasodilator response tests with both conditions, the maximal response of each individual parameter was determined and used for analyses.

2.2. Statistical analyses

Data are presented as mean ± standard deviation, median (interquartile range) or number (percentage) of patients. Patient characteristics and baseline haemodynamic parameters were compared between PAH patients and controls and between IPAH/HPAH and PAH-CHD patients, by using *t*-test for normally distributed variables, Mann–Whitney *U* test for not-normally distributed data and Chi-square test for categorical variables. Analyses were performed by using SPSS 18.0 (SPSS Inc. Chicago, IL, USA) and Stata 11 (Statacorp, College Station, Texas, USA). The level of significance was set to 0.05.

Survival analyses were based on transplant-free survival from haemodynamic evaluation, with death and transplantation as end-points. Patients without end-point were censored at last follow-up visit. Survival was evaluated by using Kaplan–Meier curves and Log Rank tests. PACi, PSVi, mSAP and heart rate were split on their median for analyses with Kaplan–Meier curves. Subsequently, the correlation of continuous haemodynamic parameters and clinical parameters (WHO-class, diagnosis, shunt, age, therapy) with survival was evaluated by using Cox regression. Backward multivariate Cox regression was used to identify the strongest haemodynamic predictors for survival. In multivariate analyses the haemodynamic predictors were corrected for clinical parameters that were associated with survival in univariate analyses. All variables met the proportionality assumptions and there were no statistical interactions between variables that were combined in multivariable analyses.

3. Results

3.1. Patient characteristics

Fifty-two paediatric PAH patients (31 female, 21 male) and 17 control patients (6 female and 11 male) were included in this study. There were 32 IPAH/HPAH and 20 PAH-CHD patients (15 with post-tricuspid shunt, 1 with pre-tricuspid shunt and 4 with corrected shunt). Median age of the PAH patients was 7.1 years. The distribution of gender, age and shunt types did not differ between the PAH patients and the control group (Table 1).

Patients were treated according to the evolving guidelines for diagnosis and treatment of pulmonary hypertension [2]. Nine patients did not receive PAH-targeted therapy because they were diagnosed and died in the era in which PAH-targeted therapy (endothelin receptor antagonist, PDE5-inhibitor or prostacyclin derivate) was not yet available in the Netherlands. There were 23 patients on mono, and 20 patients on combination (dual or triple) PAH-targeted therapy.

3.2. Haemodynamics

The PAH patients had severe PAH with elevated mPAP and PVRi (Table 2). In contrast, control subjects without a pulmonary to systemic shunt had normal mPAP, PVRi and Qpi. Control subjects with a pre- or post-tricuspid shunt had increased Qpi (median 6.9 L/min/m^2) due to left to right shunting, accompanied by a low PVRi (range 0.5–1.1 WU.m^2) and normal mPAP (range 10–17 mmHg). The mSAP of the control patients was comparable to the PAH patients, reflecting a successful patient matching procedure. The PSVi and PACi were both significantly decreased in the PAH patients compared to the controls. Except for the aorta saturation, there were no significant differences in baseline haemodynamics between the IPAH/HPAH and PAH-CHD patients. Both PSVi and PACi were lower in patients with higher WHO-functional class (Fig. 1).

41 (79%) PAH patients were tested for acute pulmonary vasodilator response. The mPAP, mPAP/mSAP and PVRi significantly decreased during acute vasodilator response (Table 3), whereas mean pulmonary arterial pulse pressure did not significantly change. Both PSVi and PACi increased significantly during acute vasodilator response testing.

Table 1
Baseline characteristics.

	All patients (n = 52)	Control patients (n = 17)	P-value*	IPAH/HPAP (n = 32)	PAH-CHD (n = 20)	P-value†
Age at right heart catheterization (yrs)	7.1 (3.1;13.3)	7.1 (3.7;12.1)	0.99	7.6 (3.8;14.0)	7.0 (2.0;11.8)	0.27
Follow-up time (yrs)	3.9 (1.6;7.0)			3.7 (0.7;7.0)	4.1 (2.6;6.9)	0.73
Sex male	21 (40)	11 (65)	0.10	16 (50)	5 (25)	0.09
WHO-Functional class						
I	1 (2)			0 (0)	1 (5)	0.82
II	17 (33)			12 (38)	5 (25)	
III	26 (50)			15 (47)	11 (55)	
IV	8 (15)			5 (16)	3 (15)	
Shunt						
No shunt	36 (69)	11 (65)	0.69	32 (100)	4 (20)	<0.01[a]
Pre-tricuspid shunt	1 (2)	1 (6)			1 (5)	
Post-tricuspid shunt	15 (29)	5 (29)			15 (75)	

Values are in median (interquartile range) or n (%) as appropriate.
Comparison between *all patients versus control patients and †IPAH/HPAH versus PAH-CHD with Mann–Whitney *U* test, Chi-square tests or Fisher's exact test as appropriate.
IPAH/HPAH, idiopathic or hereditary pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; yrs, years; WHO, World Health Organization.
[a] Significant test result.

3.3. Survival

The patients in our cohort had regular standardized follow-up visits, with a median follow-up time of 3.9 years (interquartile range 1.6–7.0 years). Considering the small number of patients with more than 7 years of follow-up (25%, 13 patients), survival analyses were truncated at 7 years of follow-up. The 1-, 2-, and 5-year survival rates of the cohort were 88%, 86%, and 68%, respectively. No difference in survival between the iPAH/HPAH and PAH-CHD patient group could be demonstrated (Fig. 2). Kaplan–Meier curves showed that a higher PSVi and a higher PACi were associated with better survival (Fig. 3A). Furthermore, higher mSAP and lower heart rate were associated with improved survival (Fig. 3B). The associations of PACi, PSVi, mSAP and heart rate with survival were not explained by differences in distribution of diagnosis, patients with HPAH or patients treated with prostacyclin derivate, between the percentile groups. Furthermore, there was no indication that the strength of these associations differed between the diagnosis subgroups.

In univariate Cox regression analyses higher PSVi, higher PACi, lower mPAP/mSAP, lower heart rate (during general anaesthesia) and higher mSAP were associated with better survival (Table 4). In contrast, mPAP, PVRI, Qpi and Qsi did not show a significant association with survival. In a backward stepwise multivariate Cox regression analysis including the haemodynamic variables that were associated with survival in univariate analysis, PSVi, heart rate and mSAP emerged as the strongest haemodynamic predictors for survival in this series of paediatric PAH.

Patients in WHO-functional class IV had worse survival compared to patients in WHO-functional classes I–III. Patients on PAH-targeted mono or combination therapy had better survival compared to patients for whom PAH-targeted therapy was not yet available. Therefore, subsequently, haemodynamic variables that were demonstrated to have an association with survival were corrected for WHO-functional class and PAH-targeted therapy in multivariate Cox regression analyses. These analyses showed that higher PSVi, higher PACi, lower heart rate, lower mPAP/mSAP and higher mSAP were associated with improved survival independent from WHO-functional class and PAH-targeted therapy (Table 4). Younger patients tended to have worse survival compared to older patients. In order to adjust the survival analysis for the effect of age on mSAP and heart rate, the multivariate analyses were additionally corrected for age (Table 4). After correction for age, the point estimates of the associations remained the same, indicating that the associations were independent from age.

Two of the IPAH/HPAH patients (6.3%) showed acute vasodilator response according to the response criteria of the ESC guidelines [2].

Table 2
Baseline haemodynamic measurements.

	All patients (n = 52)	Control patients (n = 17)	P-value*	IPAH/HPAP (n = 32)	PAH-CHD (n = 20)	P-value†
Heart rate	79 (69;106)	85 (71;98)	0.82	79 (67;107)	77 (70;104)	0.87
Aortic oxygen saturation (%)	96 (88;99)	100 (99;100)	<0.01[a]	98 (94;99)	90 (83;94)	0.01[a]
Mean right atrial pressure (mmHg)	6 (5;8)	5 (4;6)	0.03[a]	6 (5;8)	6 (5;8)	0.69
Mean pulmonary arterial pressure (mmHg)	51 ± 19	13 ± 3	<0.01[a]	51 ± 20	51 ± 16	0.95
Mean systemic arterial pressure (mmHg)	60 ± 13	63 ± 12	0.47	62 ± 13	57 ± 13	0.18
mPAP/mSAP	0.9 ± 0.3	0.2 ± 0.1	<0.01[a]	0.9 ± 0.4	0.9 ± 0.2	0.61
Pulmonary blood flow index (l/min/m^2)	2.8 (2.3;3.8)	5.5 (3.5;6.3)	<0.01[a]	2.6 (2.2;3.5)	2.9 (2.3;4.2)	0.34
Systemic blood flow index (l/min/m^2)	2.8 (2.3;3.7)	4.1 (3.4;5.4)	<0.01[a]	2.8 (2.3;3.5)	2.5 (2.3;3.8)	0.96
Qpi/Qsi	1.0 (0.9;1.0)	1.0 (1.0;1.3)	0.05	1.0 (0.9;1.0)	1.0 (0.9;1.3)	0.15
Pulmonary vascular resistance index (WU.m^2)	14.6 (7.2;22.2)	0.7 (0.6;1.0)	<0.01[a]	14.0 (7.1;26.9)	14.6 (8.3;19.0)	0.76
Systemic vascular resistance index (WU.m^2)	18.2 (13.5;22.3)	13.5 (11.6;18.3)	0.03[a]	17.7 (14.0;25.6)	18.2 (11.9;21.7)	0.46
PVR/SVR	0.8 (0.5;1.1)	0.1 (0.0;0.1)	<0.01[a]	0.8 (0.4;1.1)	0.8 (0.5;1.1)	0.96
Pulmonary stroke volume index (ml/m^2)	32.9 (27.3;44.3)	60.2 (46.1;78.6)	<0.01[a]	32.9 (26.2;42.6)	35.6 (27.9;46.4)	0.62
Pulse pressure (mmHg)	40 ± 13	10 ± 2	<0.01[a]	40 ± 14	39 ± 12	0.70
Pulmonary arterial compliance index (ml/mm Hg/m^2)	0.9 (0.6;1.3)	6.5 (4.9;7.7)	<0.01[a]	0.9 (0.6;1.2)	0.9 (0.7;1.3)	0.61

Values are in median (interquartile range) or mean ± SD as appropriate.
Comparison between *all patients versus control patients and †IPAH/HPAH versus PAH-CHD with Mann–Whitney *U* test or *T*-test for independent samples as appropriate.
IPAH/HPAH, idiopathic or hereditary pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; mmHg, millimetres of mercury; l/min/m^2, litre per minute per square metre; WU, Wood units; mPAP/mSAP, mean pulmonary to systemic pressure ratio; Qpi/Qsi, pulmonary to systemic flow ratio; PVR/SVR, pulmonary to systemic vascular resistance ratio.
[a] Significant test result.

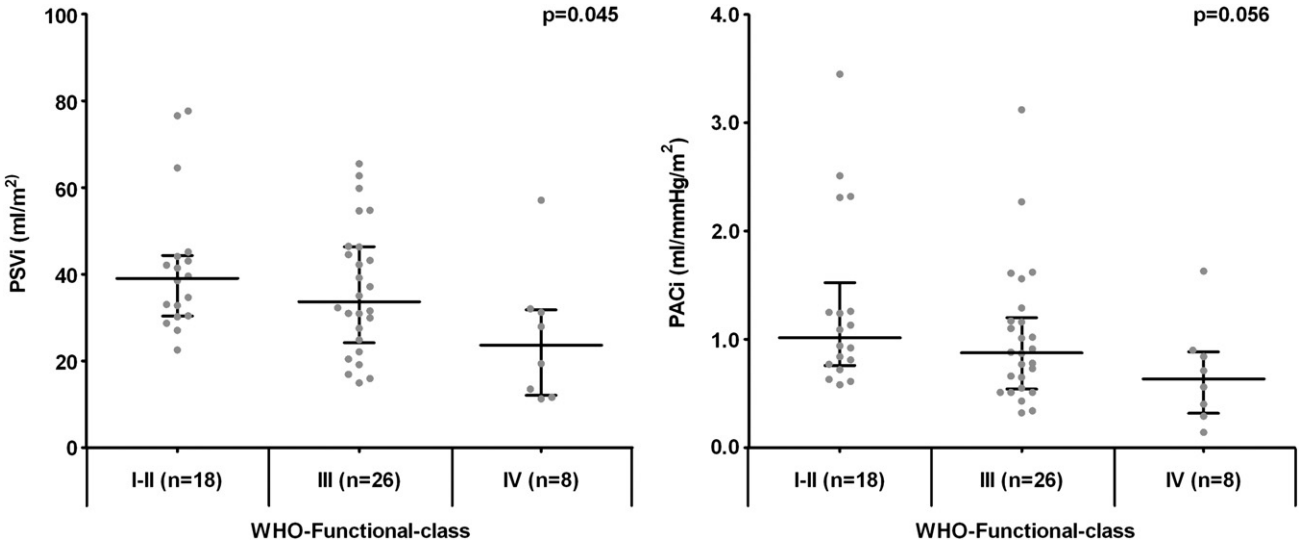

Fig. 1. PSVi and PACi for WHO-functional class subgroups. Scatter plot with indications of median and interquartile ranges of PSVi and PACi, respectively, for WHO-functional class subgroups. P-values derived from Kruskal–Wallis test. PSVi, pulmonary stroke volume index; PACi, pulmonary arterial compliance index; WHO-functional class, World Health Organization functional class.

Both patients survived during the study period and with that, responders tended to have improved survival compared to non-responders. However, individual haemodynamic variables during acute pulmonary vasodilator response testing did not provide additional information to the prognostic value of their baseline values.

4. Discussion

Despite the introduction of PAH-targeted therapy, paediatric PAH is still a severe disease with a detrimental prognosis, illustrated by reported survival rates in the current era [11,13]. Conventional haemodynamic

Table 3
Acute vasodilator response test.

		IPAH/HPAH (n = 26)	PAH-CHD (n = 15)	All patients (n = 41)	P-value
mPAP	Baseline	51 ± 21	51 ± 15	51 ± 19	
	Maximal change	−5 ± 9	−1 ± 4	−3 ± 7	
	Maximal response	46 ± 21	50 ± 16	47 ± 19	<0.01[a]
mPAP/mSAP	Baseline	0.8 ± 0.3	0.9 ± 0.2	0.9 ± 0.3	
	Maximal change	−0.1 ± 0.2	−0.0 ± 0.1	−0.1 ± 0.2	
	Maximal response	0.7 ± 0.4	0.9 ± 0.2	0.8 ± 0.4	<0.01[a]
Qpi	Baseline	2.5 (2.2;3.2)	2.7 (2.2;3.8)	2.6 (2.2;3.3)	
	Maximal change	0.2 (−0.0;0.7)	0.4 (−0.2;1.2)	0.2 (−0.0;0.7)	
	Maximal response	2.9 (2.2;3.9)	2.7 (2.2;4.9)	2.9 (2.2;4.1)	<0.01[a]
Qsi	Baseline	2.8 (2.3;3.3)	2.7 (2.3;4.2)	2.8 (2.3;3.8)	
	Maximal change	0.2 (−0.0;0.6)	−0.4 (−0.6;−0.2)	0.0 (−0.3;0.3)	
	Maximal response	2.9 (2.3;3.9)	2.4 (2.2;3.6)	2.9 (2.3;3.7)	0.73
PVRi	Baseline	14.8 (7.9;27.8)	15.7 (10.0;19.4)	15.7 (8.8;26.0)	
	Maximal change	−3.0 (−4.9;−0.9)	−1.7 (−6.3;0.4)	−2.9 (−4.9;−0.9)	
	Maximal response	10.1 (4.1;20.1)	14.8 (6.7;24.4)	11.7 (5.1;20.1)	<0.01[a]
PVR/SVR	Baseline	0.8 (0.5;1.1)	0.9 (0.6;1.4)	0.9 (0.5;1.1)	
	Maximal change	−0.2 (−0.3;−0.1)	−0.2 (−0.5;0.0)	−0.2 (−0.3;−0.0)	
	Maximal response	0.6 (0.3;0.8)	0.6 (0.4;0.9)	0.6 (0.3;0.9)	<0.01[a]
PSVi	Baseline	32.5 (27.5;41.5)	30.4 (22.5;43.2)	32.0 (27.1;42.1)	
	Maximal change	4.8 (2.3;8.7)	6.1 (−0.2;12.7)	5.3 (2.2;9.9)	
	Maximal response	39.1 (33.2;52.3)	37.2 (26.5;46.5)	38.6 (31.3;48.4)	<0.01[a]
PAPP	Baseline	40 ± 14	38 ± 13	39 ± 14	
	Maximal change	−3.7 ± 11.8	0.5 ± 4.5	−2.2 ± 9.9	
	Maximal response	36 ± 17	39 ± 12	37 ± 15	0.16
PACi	Baseline	0.9 (0.6;1.1)	0.8 (0.6;1.3)	0.8 (0.6;1.1)	
	Maximal change	0.1 (0.1;0.5)	0.1 (−0.0;0.3)	0.1 (0.1;0.4)	
	Maximal response	1.0 (0.8;2.2)	0.9 (0.7;1.4)	1.0 (0.8;1.5)	<0.01[a]

Values are in median (interquartile range) or mean ± SD as appropriate. Comparison between baseline and maximal vasodilator responses in the all patients group with Wilcoxon signed rank test or paired *T*-test as appropriate.
mPAP, mean pulmonary arterial pressure; mPAP/mSAP, mean pulmonary to systemic pressure ratio; Qpi, pulmonary flow index; Qsi, systemic flow index; PVRi, pulmonary vascular resistance index; PVR/SVR, pulmonary to systemic vascular resistance ratio; PSVi, pulmonary stroke volume index; PAPP, pulmonary arterial pulse pressure; PACi, pulmonary arterial compliance index.
[a] Significant test result.

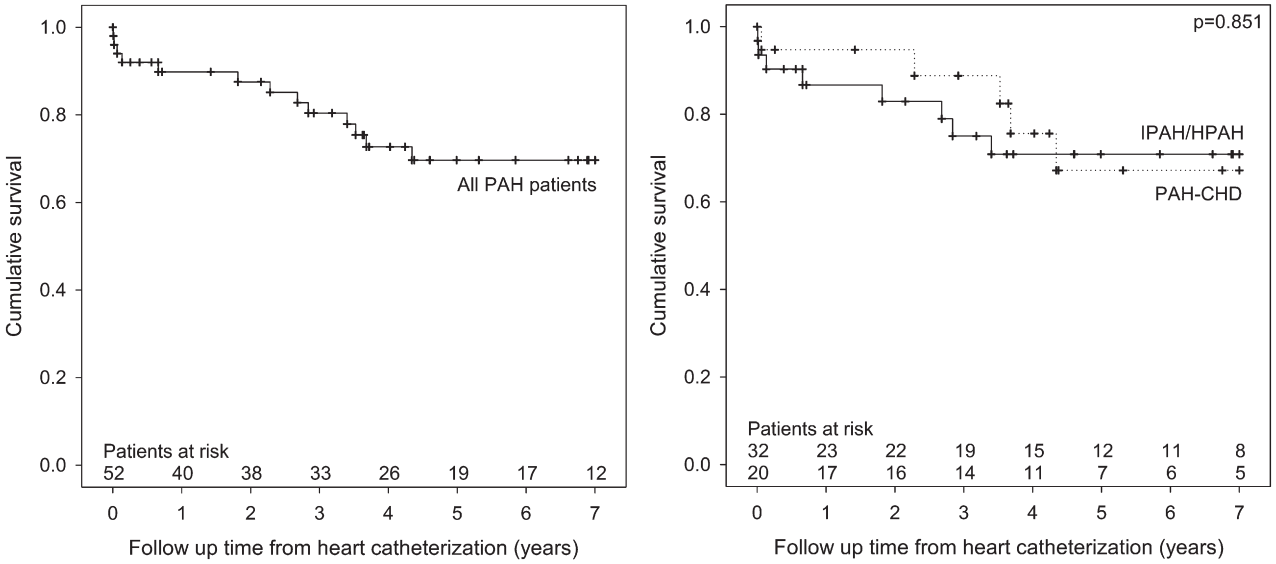

Fig. 2. Survival of the study group. Kaplan–Meier curves showing the survival of all included PAH patients (left) and stratified for diagnosis subgroup (right). PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; IPAH/HPAH, idiopathic or hereditary pulmonary arterial hypertension.

parameters represent only the static part of RV afterload and provide limited prognostic information. This study shows that pulsatile components of RV afterload provide important additional prognostic information.

The predictive value of PACi and PSVi for survival can be explained by their increasingly important role in pulsatile flow and RV afterload in PAH [16]. High compliant pulmonary arteries can reduce pulmonary arterial pressures and flow velocities, thereby delaying reflecting pressure waves. Reduced compliance leads to higher pressures, higher flow rate and early reflection waves, thereby increasing RV workload, which ultimately results in RV failure. Therefore in PAH, PACi reflects an important part of the RV afterload.

Since PACi and PVRi determine the ability of the pulmonary arteries to accommodate blood flow, a reduced PACi and increased PVRi leads to reduced PSVi. Increased RV afterload and the accompanying increased RV work load and hypertrophy in PAH, may eventually decrease PSVi even further [27]. One could question whether the association between PSVi and survival is driven by RV function or by progression of the pulmonary vascular disease. This is a complex issue, especially in a patient group with heterogeneous complex congenital heart diseases. The current data show that the association of PSVi with outcome was found not only in IPAH/HPAH, but also in PAH-CHD patients with a shunt at post-tricuspid level. In the latter patient group, PSVi is not synonymous to RV stroke volume due to right to left shunting and thus PSVi does not simply reflect RV function. In patients with intracardiac shunts, PSVi was associated with survival. Furthermore, there was no indication that the strength of the found associations with survival in PAH-CHD patients differed from that in iPAH/HPAH patients. These findings support the notion that PSVi seems to represent a function of pulmonary vascular disease rather than of RV function.

PACi and PSVi both reflect disease severity in paediatric PAH. They are likely to decrease during disease progression of PAH and are candidate-parameters to assess disease severity and treatment effects. PSVi may more fully represent the progression of the vascular disease than PACi, since PSVi is determined by the RV afterload as a whole, including vascular resistance, arterial compliance and reflection waves, whereas PACi predominantly represents pulmonary arterial compliance. This may explain why our analyses indicates that PSVi is the stronger prognostic parameter in paediatric PAH compared to PACi.

Higher PACi was associated with improved survival independent from WHO-functional class and therapy, which is in congruence with previous reports in adult PAH [18,19]. Sajan et al. [28] showed that in children with PAH, worse survival was predicted by either a higher or a lower than average PACi. In contrast, in the present study, the association between PACi and survival showed to be more linear. The reason for this disparity may lay in the difference in the composition of the study groups. Sajan et al. [28] included a large group of PAH-CHD patients with high PACi and it was unclear whether these patients all had advanced, irreversible PAH, whereas in the current study, all PAH-CHD patients had advanced irreversible PAH.

Higher PSVi was associated with improved survival in our study. RV stroke volume measured by pulmonary arterial MRI or by Fick's method has previously been shown to be a valuable prognostic factor in adult IPAH/HPAH [20]. In earlier reports cardiac index has been shown to be a prognostic parameter in iPAH. However, PSVi showed to be a stronger predictor of survival in both paediatric and adult PAH [4,13,20]. This can be explained by the fact that a decreased PSVi can be compensated by an increased heart rate, thereby maintaining cardiac output. The latter will affect the association of cardiac index with survival [20]. This notion is supported by the association of higher heart rate with decreased survival as found in the current study.

The investigated patient cohort included patients for whom advanced PAH therapy was not yet available. Evolving treatment strategies may influence outcome and survival analyses. The analyses were corrected for this potentially confounding effect of treatment and the prognostic value of PACi and PSVi showed to be independent from treatment. This indicates that these associations were not affected by the evolving treatment strategies.

In this study the conventional, static parameters mPAP and PVRi were not associated with survival. PVRi and mPAP are important objective parameters in the confirmation of the diagnosis and assessment of disease severity in PAH. Although reports on the prognostic value of mPAP and PVRi in PAH are inconsistent, several studies in paediatric PAH have shown a lack of significant prognostic value of mPAP and/or PVRi in these patients. In paediatric PAH, PACi and PSVi appeared to be stronger predictors of survival compared to mPAP and PVRi. Therefore, in the clinical situation PACi and PSVi can provide prognostic information additional to conventional haemodynamic measurements, potentially improving goal-oriented treatment strategies.

In addition to PACi and PSVi, lower mPAP/mSAP, lower heart rate, and higher mSAP were associated with improved survival in our study. The association of mPAP/mSAP with survival is in congruence

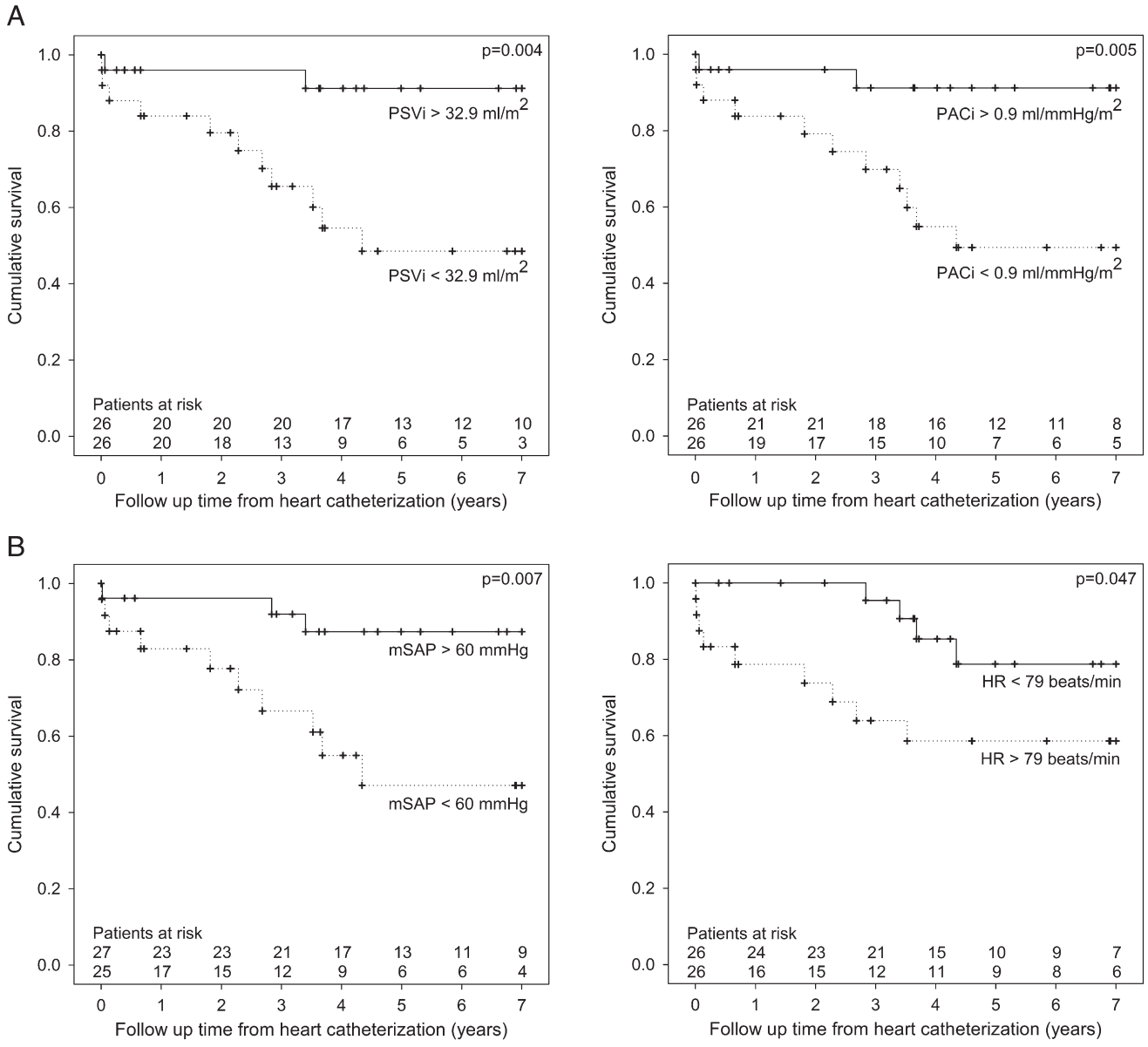

Fig. 3. A) Survival stratified for PSVi and PACi. Kaplan–Meier curves with log rank tests showing the survival of all included PAH patients stratified for the median of pulmonary stroke volume index (PSVi, left) and pulmonary arterial compliance index (PACi, right). B) Survival stratified for mSAP and heart rate Kaplan–Meier curves with log rank tests showing the survival of all included PAH patients stratified for the median of mean systemic arterial pressure (mSAP, left) and heart rate (HR, right).

with previous reports, showing that high mPAP/mSAP is associated with poorer outcome in paediatric PAH [13,29]. Since the associations of PACi and PSVi with survival were more stable in multivariate analysis than that of mSAP, mPAP/mSAP and heart rate, these pulsatile parameters seem to have a stronger prognostic value.

Heart rate and mSAP are affected by children's age, which by itself is associated with outcome in paediatric PAH [12]. Therefore age may partially explain their association with survival. In this study, the point estimates of the survival analyses remained numerically the same when corrected for age. Therefore the associations of heart rate, PACi, PSVi, mSAP and mPAP/mSAP with survival appear age independent.

The association of heart rate with survival, previously reported in adult PAH, may provide important clinical advantages [30,31]. Heart rate is a non-invasive, easily obtainable parameter suitable for multiple follow-up measurements in paediatric PAH. Therefore heart rate may potentially be a valuable parameter to assist in guiding therapy in paediatric PAH.

Heart rate may both determine and respond to stroke volume of the RV, LV or both combined and with that it is strongly related with PSVi. Despite this intimate relation, both parameters appeared independent predictors of survival in this study. Therefore both parameters may have complementary value in guiding treatment.

4.1. Study limitations

Our analyses were limited by the relatively small number of patients. Nevertheless, we found strong correlations between survival and the pulsatile haemodynamic variables. In paediatric pulmonary hypertension, a very rare disease, patient numbers and data regarding survival and prognostic parameters are extremely limited. Therefore this study contributes largely to the currently available data.

Furthermore, no paired case-control matching could be performed due to the low number of available control patients. Congenital heart defects associated with systemic to pulmonary shunts and low PVRi are currently corrected at an early age before PVRi rises, leaving virtually no older patients with an important shunt and low PVR. Therefore a frequency matching approach was applied.

Table 4
Cox regression analyses for transplant-free survival.

	Univariate analyses		Multivariate analyses†		Multivariate analyses‡	
	HR (95%-CI)	P-value	HR (95%-CI)	P-value	HR (95%-CI)	P-value
Mean pulmonary arterial pressure[b]	1.01 (0.98–1.04)	0.533				
Mean systemic arterial pressure[b]	0.94 (0.89–0.99)	0.016[a]	0.93 (0.86–1.00)	0.042[a]	0.95 (0.88–1.02)	0.186
mPAP/mSAP ratio[c]	1.34 (1.07–1.68)	0.010[a]	1.44 (1.41–1.82)	0.002[a]	1.36 (1.05–1.77)	0.020[a]
Pulmonary vascular resistance index[d]	1.03 (0.99–1.07)	0.121				
Pulmonary blood flow index[e]	0.79 (0.46–1.34)	0.374				
Systemic blood flow index[e]	0.62 (0.32–1.21)	0.159				
Pulmonary arterial compliance index[f]	0.84 (0.72–0.98)	0.027[a]	0.81 (0.68–0.98)	0.031[a]	0.83 (0.68–1.01)	0.063
Pulmonary stroke volume index[g]	0.70 (0.55–0.89)	0.004[a]	0.70 (0.53–0.93)	0.014[a]	0.73 (0.54–0.98)	0.034[a]
Heart rate[h]	1.36 (1.14–1.63)	0.001[a]	1.51 (1.16–1.97)	0.002[a]	1.43 (1.02–2.00)	0.040[a]
WHO-class IV vs. I–III	3.41 (1.11–10.43)	0.032[a]				
Therapy						
No therapy	Reference group					
Mono therapy	0.33 (0.10–1.04)	0.059				
Combination therapy	0.05 (0.01–0.44)	0.007[a]				
Age[i]	0.89 (0.79–1.00)	0.056				

Univariate and multivariate Cox regression analyses. Haemodynamic variables with a significant relation to survival in univariate test, were separately corrected for †therapy and WHO-class and ‡therapy, WHO-class, and age. mPAP/mSAP, mean pulmonary to systemic pressure ratio; WHO, World Health Organization. HR, hazard ratio.

[a] Significant test result.
[b] HR per 1 mmHg change in pressure.
[c] HR per 0.1 change in mPAP/mSAP.
[d] HR per 1 WU.m^2 change in PVRi.
[e] HR per 1 ml/m^2 change in flow index.
[f] HR per 0.1 ml/mmHg change in PACi.
[g] HR per 5 ml change in PSVi.
[h] HR per 10 bpm change in heart rate.
[i] HR per 1 year change in age.

5. Conclusions

In conclusion, parameters of the pulsatile pulmonary circulation, such as PACi and PSVi, are associated with disease severity and predict survival in paediatric PAH, independent from conventional clinical prognostic parameters, such as PVRi. Therefore these parameters can be of complementary value to more conventional haemodynamic parameters in assessing disease severity, predicting survival and guiding treatment in paediatric PAH.

References

[1] Berger RM, Bonnet D. Treatment options for paediatric pulmonary arterial hypertension. Eur Respir Rev 2010;19:321–30.
[2] Authors/Task Force Members, Galie N, Hoeper MM, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–537.
[3] Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. Eur Respir J 2005;26:858–63.
[4] D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343–9.
[5] Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780–8.
[6] Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358:1119–23.
[7] Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000;161:487–92.
[8] Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012;379:537–46.
[9] Hoeper MM, Oudiz RJ, Peacock A, et al. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. J Am Coll Cardiol 2004;43:48S–55S.
[10] McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477–82.
[11] Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart 2010;96:1401–6.
[12] Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 2012;125:113–22.
[13] van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol 2010;106:117–24.
[14] Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol 2010;106:1332–8.
[15] Lankhaar JW, Westerhof N, Faes TJ, et al. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol 2006;291:H1731–7.
[16] Sniderman AD, Fitchett DH. Vasodilators and pulmonary arterial hypertension: the paradox of therapeutic success and clinical failure. Int J Cardiol 1988;20:173–81.
[17] Wang Z, Chesler NC. Pulmonary vascular wall stiffness: an important contributor to the increased right ventricular afterload with pulmonary hypertension. Pulm Circ 2011;1:212–23.
[18] Mahapatra S, Nishimura RA, Oh JK, McGoon MD. The prognostic value of pulmonary vascular capacitance determined by Doppler echocardiography in patients with pulmonary arterial hypertension. J Am Soc Echocardiogr 2006;19:1045–50.
[19] Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol 2006;47:799–803.
[20] van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J 2007;28:1250–7.
[21] Gan CT, Lankhaar JW, Westerhof N, et al. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. Chest 2007;132:1906–12.
[22] Berger RM, Cromme-Dijkhuis AH, Hop WC, Kruit MN, Hess J. Pulmonary arterial wall distensibility assessed by intravascular ultrasound in children with congenital heart disease: an indicator for pulmonary vascular disease? Chest 2002;122:549–57.
[23] Friedberg MK, Feinstein JA, Rosenthal DN. Noninvasive assessment of pulmonary arterial capacitance by echocardiography. J Am Soc Echocardiogr 2007;20:186–90.
[24] Hunter KS, Lee PF, Lanning CJ, et al. Pulmonary vascular input impedance is a combined measure of pulmonary vascular resistance and stiffness and predicts clinical outcomes better than pulmonary vascular resistance alone in pediatric patients with pulmonary hypertension. Am Heart J 2008;155:166–74.
[25] LaFarge CG, Miettinen OS. The estimation of oxygen consumption. Cardiovasc Res 1970;4:23–30.
[26] Krovetz LJ, Goldbloom S. Normal standards for cardiovascular data. I. Examination of the validity of cardiac index. Johns Hopkins Med J 1972;130:174–86.
[27] Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. Eur Respir J 2002;20:1314–31.
[28] Sajan I, Manlhiot C, Reyes J, McCrindle BW, Humpl T, Friedberg MK. Pulmonary arterial capacitance in children with idiopathic pulmonary arterial hypertension

and pulmonary arterial hypertension associated with congenital heart disease: relation to pulmonary vascular resistance, exercise capacity, and survival. Am Heart J 2011;162:562–8.
[29] Douwes JM, van Loon RL, Hoendermis ES, et al. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: occurrence and prognostic value when comparing three response criteria. Eur Heart J 2011;32:3137–46.
[30] Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164–72.
[31] Henkens IR, Van Wolferen SA, Gan CT, et al. Relation of resting heart rate to prognosis in patients with idiopathic pulmonary arterial hypertension. Am J Cardiol 2009;103:1451–6.